Supplementary material

Real-world mepolizumab in the prospective severe asthma REALITI-A study – initial analysis

Harrison T, et al.

Corresponding author: Peter Howarth

Contents

Supplementary Information

Supplementary Information

Study design

The assignment of a patient to a particular therapeutic strategy was not decided in advance by the study protocol but was determined by the usual practice of medicine. The decision to prescribe a particular drug was also clearly dissociated from the decision to include the patient in the study. No visits were scheduled specifically for this observational study, and data were collected at usual asthma healthcare visits (routine or unscheduled). All data captured for the 12 months pre-enrolment and during the study period were entered into an electronic case report form (eCRF) as part of the routine healthcare visit. To avoid enrolment bias, sites were expected to enrol all eligible patients who presented at their site and to maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrolment of otherwise eligible patients.

Maintenance OCS dose

Maintenance OCS use in the pre-treatment period was defined as the mean daily maintenance OCS dose (expressed as prednisone equivalent dose, mg/day) in the period including the index date and the 27 days pre-index, or any other 27-day period within a maximum of 6 months pre-index if no records existed 27 days immediately pre-index.

The approach to impute the daily maintenance OCS dose as 0 mg in this study if there were gaps in the dates recorded on the eCRF was based on the fact that that the eCRF requested all instances of OCS dose use between the visits to be recorded. Data collection is based on patient recall, and querying data gaps can therefore be impossible and/or unreliable since a patient may have withdrawn from the study or a patient may not be able to recall information owing to the length of elapsed time.

Analysis: withdrawal rate

The sample size calculation was based on data from the mepolizumab COSMOS extension study (MEA115661/NCT01842607)[1], where 159 participants who received placebo in the MENSA study (MEA115588/NCT01691521)[2] switched to mepolizumab in the COSMOS study and completed both studies. A total of 25% of participants were assumed to withdraw over the course of the study, 20% in the first and 5% in the second year. Following these assumptions, a study with 12 months of mepolizumab treatment designed to detect a 35% decrease with 90% power at the two-sided 5% level would require approximately 200 participants (with an assumed dispersion parameter of 0.8).

References
[1] Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther* 2016; 38: 2058–2070.
[2] Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371(13): 1198-1207.

Clinically significant exacerbations according to maintenance OCS use and dose, age and prior omalizumab use

When assessed by maintenance OCS at enrolment ('never', 'current or past'), the reduction in clinically significant exacerbations with mepolizumab treatment, compared with the pre-mepolizumab treatment period, was similar (69% reduction in both subgroups) (**Supplementary Figure 1**). However, it should be noted that exacerbations were higher in the pre-mepolizumab treatment period in the 'current or past' subgroup compared with the 'never' subgroup. Those on low-dose (<10 mg/day) OCS at enrolment experienced a 65% reduction in exacerbations and those on high-dose (≥10 mg/day) OCS a 59% reduction (**Supplementary Figure 1**). Older age did not impact the effectiveness of mepolizumab in the real world, since reductions in the clinically significant exacerbation rate were similar in patients aged <65 and ≥65 years of age (68%–72% reductions) (**Supplementary Figure 1**). The reductions in exacerbations with mepolizumab were 60% and 71% in those with and without prior use of omalizumab therapy, respectively (**Supplementary Figure 1**).

BEC at baseline and during follow-up according to maintenance OCS use and dose

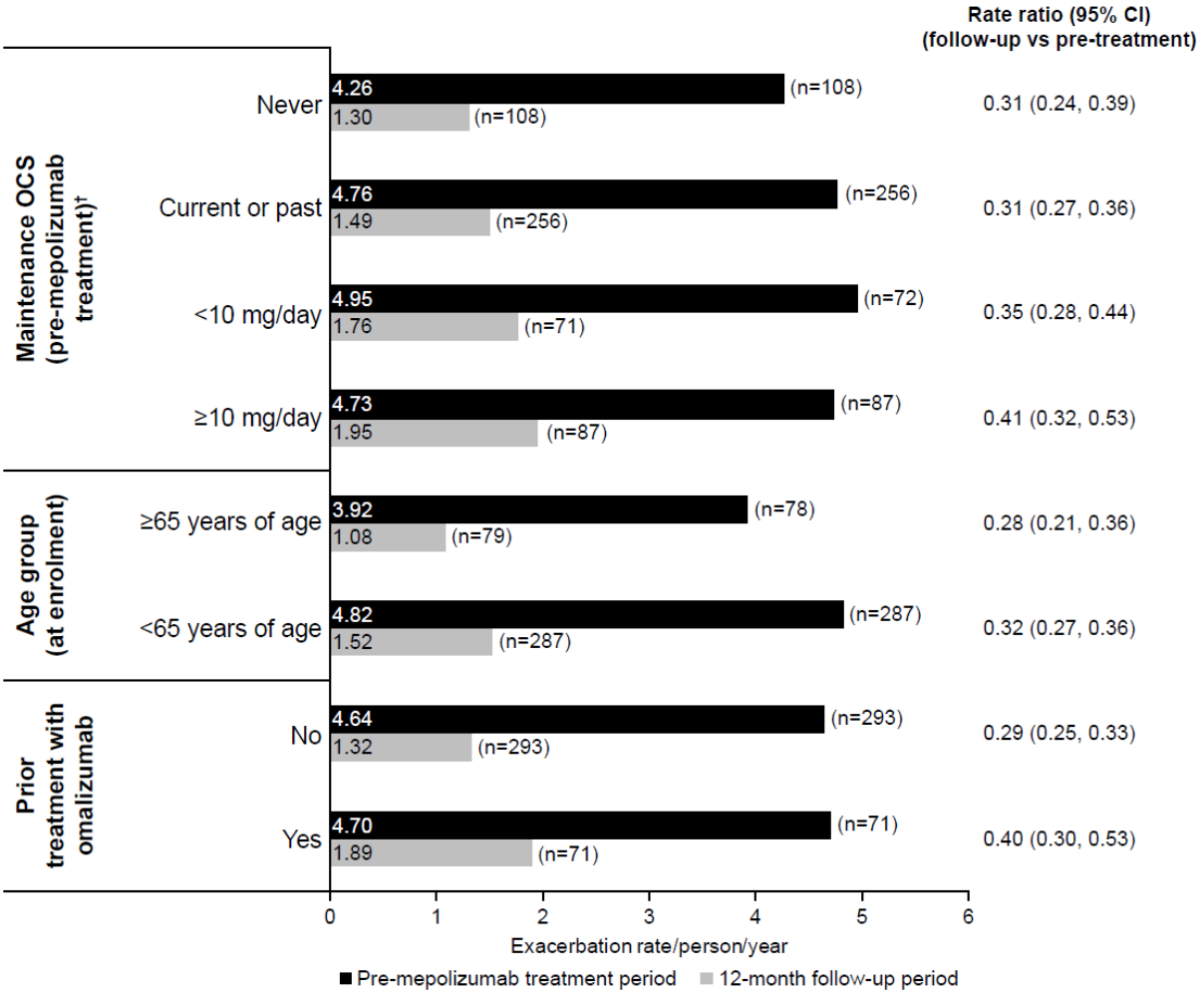
Patients receiving OCS at baseline had lower baseline BEC than those not receiving OCS. Patients receiving high-dose OCS at baseline had lower baseline BEC compared with those on low-dose OCS at baseline. Compared with baseline, mepolizumab treatment reduced BECs by 86%, 75% and 77% at months 9–12 in those not receiving OCS, and in those receiving low-dose (<10 mg/day) and high-dose (≥10 mg/day) OCS, respectively (**Supplementary Table 2**). These reductions occurred by months 0–3 and were maintained throughout the 12-month follow-up.

Supplementary Table 1. Reasons for discontinuation from the study

Reason for discontinuation	**Patients, n (%)** **N=368**
Total	70 (19)
Participant decision	27 (7)
Investigator discretion	14 (4)
Reported lack of efficacy	13 (4)
AEs	8 (2)
Other reasons	7 (2)
Missing	1 (<1)

AE, adverse event.

Supplementary Figure 1. Clinically significant asthma exacerbation rates in the pre-mepolizumab-treatment period* and 12-month follow-up period according to maintenance OCS use and dose, age at enrolment and prior omalizumab use



*365 days prior to enrolment plus any exacerbations starting during run-in. †During the period including the index date and the 27 days prior to index, or any other 27-day period in the last 6 months if no records existed 27 days immediately prior to index.

CI, confidence interval; OCS, oral corticosteroid.

Supplementary Table 2. Baseline BEC and 12-month follow-up period according to maintenance OCS use and dose in the in the pre-mepolizumab-treatment period* and 12-month follow-up period

	BEC, cells/µL	
Maintenance OCS status at baseline	**Baseline**	**Follow-up period (at month 9–12)**
Not receiving (n=108)		
Geo mean (±SD log)	412 (1.092)	–
Median (Q1, Q3)	500 (315, 800)	–
LS geo mean at month 9–12 (95% CI)	410 (330, 510)	60 (40, 90)
LS mean ratio to baseline at month 9–12 (95% CI)	–	0.14 (0.08, 0.22)
Receiving* (n=257)		
Geo mean (±SD log)	352 (1.308)	–
Median (Q1, Q3)	410 (240, 800)	–
LS geo mean at month 9–12 (95% CI)	350 (300, 410)	60 (50, 80)
LS mean ratio to baseline at month 9–12 (95% CI)	–	0.18 (0.14, 0.24)
Receiving <10 mg/day (n=72)		
Geo mean (±SD log)	352 (1.118)	–
Median (Q1, Q3)	384 (245, 740)	–
LS geo mean at month 9–12 (95% CI)	350 (270, 450)	90 (60, 130)
LS mean ratio to baseline at month 9–12 (95% CI)	–	0.25 (0.16, 0.38)
Receiving ≥10 mg/day (n=87)		
Geo mean (±SD log)	234 (1.460)	–
Median (Q1, Q3)	300 (190, 600)	–
LS geo mean at month 9–12 (95% CI)	230 (180, 310)	60 (30, 90)
LS mean ratio to baseline at month 9–12 (95% CI)	–	0.23 (0.13, 0.41)

*Also includes patients with past use of maintenance OCS (>26 weeks of a year).

BEC, blood eosinophil count; CI, confidence interval; Geo, geometric; LS, least squares; OCS, oral corticosteroids; SD, standard deviation; Q, quartile.